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REMARKS

Claims 12-25, 27, 29 and 31-40 are pending in this application. Claims 12-24 have been withdrawn. Claims 25, 29, 32-34, 36, and 37 are currently amended. Claim 28 is canceled, without prejudice or disclaimer. New claims 39 and 40 are added.

Claims 25 and 36 are amended in matters of form and to clarify that the claim is directed to a method as performed by the recited steps.

Claims 25 and 36 are further amended to indicate that the DNA chip comprises a combination of at least two different probes selected from the group consisting of SEQ ID NOs:1-19. This amendment is fully supported by the application as filed. See, for example, page 9, line 21 through page 10, line 27 and, especially, page 9, lines 13-19.

Claim 29 is amended to recite the that the primer pair may be selected from the group consisting of GP5+ (SEQ ID NO: 22), GP6+ (SEQ ID NO: 23), GP5d+ (SEQ ID NO: 24), and GP6d+ (SEQ ID NO: 25). This amendment is fully supported by the specification as filed. See, for example, page 11, lines 26-32.

Claims 32, 33, and 34 are amended to replace the phrase "a solid support" with the phrase "the glass slide". These amendments are fully supported by the specification as filed. See for example, page 7, lines 27-29 and page 10 lines 13-27.

Claim 37 is amended to correct a typographical error in the spelling of "streptavidin".

New claims 39 and 40 are added. These claims are fully supported by the specification as filed. See, for example, page 18, lines 21-29, and in particular, page 9, line 21 through page 10, line 27.

Thus, none of the amendments introduces new matter to the application. Entry and consideration of the amendments is therefore respectfully requested.

I Telephonic interview of August 10, 2005

Applicants again gratefully acknowledge the Examiner's courtesy in holding a telephonic interview regarding this case on March 10, 2006. This interview was held between Examiner Tung at the Patent Office and Mr. Ludwig (Reg No. 25,351) and Dr. Goldin (Reg. No 54,127) as attorneys/agents of record.

In this interview, an amendment of claim 25 was discussed. The amended form of claim 25 as discussed during the interview was as follows:

25. (Currently amended) A method for diagnosis of Human Papillomavirus (HPV) infection ~~using an HPV genotyping kit,~~ comprising:

(a) amplifying DNA obtained from clinical samples with the primers of an HPV genotyping kit to obtain biotin-containing amplified DNA, wherein the HPV genotyping kit comprises:

(i) a DNA chip comprising at least two different ~~probes having an~~ HPV nucleic acid sequence probes ~~set forth in SEQ ID NO: 1~~ selected from the group consisting of:

SEQ ID NO: 1 ~~and~~ or the complementary ~~sequences~~ sequence thereof;

SEQ ID NO: 2 or the complementary sequence thereof;

SEQ ID NO: 3 or the complementary sequence thereof;

SEQ ID NO: 4 or the complementary sequence thereof;

SEQ ID NO: 5 or the complementary sequence thereof;

SEQ ID NO: 6 or the complementary sequence thereof;

SEQ ID NO: 7 or the complementary sequence thereof;

SEQ ID NO: 8 or the complementary sequence thereof;

SEQ ID NO: 9 or the complementary sequence thereof;

SEQ ID NO: 10 or the complementary sequence thereof;

SEQ ID NO: 11 or the complementary sequence thereof;

SEQ ID NO: 12 or the complementary sequence thereof;

SEQ ID NO: 13 or the complementary sequence thereof;

SEQ ID NO: 14 or the complementary sequence thereof;

SEQ ID NO: 15 or the complementary sequence thereof;

SEQ ID NO: 16 or the complementary sequence thereof;

SEQ ID NO: 17 or the complementary sequence thereof;

SEQ ID NO: 18 or the complementary sequence thereof; and

SEQ ID NO: 19 or the complementary sequence thereof,

and a glass slide to which the probes are attached;

(ii) biotin-labeled primers for amplifying DNA obtained from clinical samples; and

(iii) means for labeling amplified DNA that hybridizes with the probes of the DNA ~~chip,~~ chip;

~~which method comprises:~~

~~(a) amplifying DNA obtained from clinical samples with the primers of the HPV genotyping kit to obtain biotin-containing amplified DNA;~~

(b) applying the amplified DNA to the DNA chip under conditions which allow hybridization of the amplified DNA to the probes;

(c) applying a biotin-binding label to the hybridized DNA on the chip; and

(d) detecting hybridized DNA on the surface of the DNA chip by detecting the a biotin-binding label,

wherein detection of the biotin-binding label indicates the presence of HPV DNA in the sample which corresponds to the HPV probe to which the DNA is hybridized.

Examiner Tung indicated that such an amendment to claim 25 would be entered in this case, provided that appropriate support for the amendment was identified in this response.

It was further discussed that the purpose of the amendment was to clarify that the DNA chip recited in the claimed method contains a combination of multiple HPV nucleic acid probes, rather than a single HPV nucleic acid probe. The Examiner was informed that the amended claim 25 to be presented in the response to the outstanding official action would recite "a DNA chip comprising a combination of at least two different HPV nucleic acid sequence probes", in further emphasis of this point.

II. Restriction Requirement

Applicants gratefully acknowledge Examiner's statement that the election of the probe of SEQ ID NO: 1, and primer pair of SEQ ID NO:22 and 23, is withdrawn. The Examiner has suggested amending the claim language to indicate that a combination of SEQ ID NO:1-19 is used to make an array for the claimed method.

Accordingly, claims 25 and 36 are amended to indicate that the DNA chip comprises a combination of at least two different probes selected from the group consisting of SEQ ID NOs:1-19. This amendment is fully supported by the application as filed (see, for example, page 9, line 21 through page 10, line 27 and page 9, lines 13-19). The Examiner's attention is particularly drawn to page 9, lines 13-19, which discloses that the DNA chips to be used in the methods of the invention may comprise any number of HPV probes. The claim language has been restricted to reciting a combination of "*at least two probes*" (emphasis added) so that the claim properly defines a combination as requested by the Examiner (*i.e.*, a DNA chip with only one probe would not constitute a "combination" of probes, at least two different probes are necessary to define a "combination").

Similarly, new claims 39 and 40 are added. These claims are directed to specific embodiments of the method of the invention, wherein the DNA chip comprises a combination of *each* of the HPV nucleic acid probes of SEQ ID NOs:1-19 (*i.e.*, a combination of 19 different HPV probes). The claims are fully supported by the specification as filed (see, for example, page 18, lines 21-29, and in particular, page 9, line 21 through page 10, line 27).

Furthermore, Claim 29 is amended to recite the that the primer pair may be selected from the group consisting of GP5+ (SEQ ID NO: 22), GP6+ (SEQ ID NO: 23), GP5d+ (SEQ ID

NO: 24), and GP6d+ (SEQ ID NO: 25), thus restoring the previously deleted non-elected primers of GP5d+ and GP6d+ to the claim. This amendment is fully supported by the specification as filed (see, for example, page 11, lines 26-32).

III. The Claim Rejections Under 35 U.S.C. § 112 Should Be Withdrawn

The Examiner has rejected claims 28 and 32-35 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 28 has been canceled, without prejudice or disclaimer.

Claims 32, 33, and 34 have been amended to replace the phrase "a solid support" with the phrase "the glass slide".

Thus, the basis for the Examiner's rejection is believed to have been overcome. Applicant's therefore respectfully request that this rejection be withdrawn.

IV. The Claim Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 25, 27, 29, 32-34 and 36-37

The Examiner has rejected claims 25, 27, 29, 32-34 and 36-37 under 35 U.S.C. § 103(a) as unpatentable over Meijer *et al* (WO 95/22626, hereafter "Meijer"), in view of Day *et al. Biochem J.* 1990;267:119-123 (hereafter "Day") and Lukhtanov *et al.* (US 6,339,147, hereafter Lukhtanov).

Meijer teaches a method for diagnosis of HPV infection comprising the steps of (i) amplification of HPV DNA from clinical samples using the primers GP5+ and GP6+; (ii) electrophoresis of the amplified DNA; (iii) transfer of the amplified DNA to a Southern Blot; (iv) hybridization of this Southern Blot with HPV-specific oligonucleotide probes, either singly or as a probe cocktail comprised of multiple individual probes; and (v) detection of the hybridized HPV-specific oligonucleotide probes. Thus, in this method the amplified DNA is immobilized and the oligonucleotides serve as detection agents hybridized to the immobilized amplified DNA (see, *e.g.*, page 21, lines 21-26 and page 30, line 5 through page 31, line 3 of Meijer).

This *method is different from that of the presently claimed invention*, which comprises the steps of (i) amplifying DNA from clinical samples using primers, such a GP5+ and GP6+ to obtain biotin-containing amplified DNA; (ii) hybridization of this biotin-labeled

DNA to a DNA chip comprising a combination of a least two different HPV-specific oligonucleotide probes immobilized on a glass slide; and detecting hybridized DNA on the DNA chip. Thus, in the method of the present invention the HPV-specific oligonucleotide probes are immobilized on a glass slide and the amplified DNA serves as a detection agent hybridized to the immobilized HPV-specific oligonucleotide probes.

This difference in the two methods is not trivial, for at least the reason that each method results in vastly different hybridization kinetics. In the method of Meijer the immobilized nucleic acid sequence is significantly larger, approximately 5 fold larger, than that of the hybridized nucleic acid. Specifically, the size of DNA amplified by the primers GP5+ and GP6+ is approximately 150 nucleotides (see at Exhibit A Genbank entry AF548859 for the partial DNA sequence of HPV type 51 showing the position of each primer of the pair), while the HPV-specific oligonucleotides are each only 30 nucleotides in length (see oligonucleotides a through x as set forth on pages 15-16 of Meijer). Conversely, in the method of the present invention, the immobilized nucleic acid (the HPV-specific oligonucleotides, each of which is 30 nucleotides in length, see SEQ ID NOs:1-19) is significantly smaller that the hybridized nucleic acid (the biotin-labeled amplified DNA, which is approximately 150 nucleotides in length, as discussed for Meijer).

One of skill in the art would readily appreciate that this difference in the size of the immobilized nucleic acid (~150 nucleotides in the method of Meijer versus 30 nucleotides in the method of the invention) would have significant effects on the hybridization kinetics of each method (see, *e.g.*, the abstract of Stillman and Tonkinson. *Anal Biochem* 2001;295:149-157 provided as Exhibit B). For at least this reason (*i.e.*, difference in hybridization kinetics due to size of immobilized nucleic acid), one of ordinary skill in the art would not assume that the method of Meijer would still work if the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide.

One of skill in the art would further appreciate that the difference in the size of the hybridized nucleic acid (~30 nucleotides in the method of Meijer versus ~150 nucleotides in the method of the invention) would have significant effects on the hybridization kinetics of each method (see, *e.g.*, the abstract of Chan *et al. Bio phys J* 1995;69:2243-2255 provided as Exhibit C). For at least this reason (*i.e.*, difference in hybridization kinetics due to size of hybridized nucleic acid), one of ordinary skill in the art would not assume that the method of Meijer would

still work if the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide. On the contrary, Chan *et al.* teaches away from the present invention in that it teaches that the hybridized nucleic acid should be about 100 nucleotides or less, whereas in the method of the present invention the hybridized nucleic acid is about 150 nucleotides. Thus, one of ordinary skill in the art would not be motivated to alter the method of Meijer to provide a method wherein the amplified DNA was hybridized to an immobilized HPV-specific oligonucleotide.

Neither Day nor Lukhtanov provides teaching to remedy this deficiency of Meijer. Specifically, neither Day nor Lukhtanov provides teaching regarding hybridization kinetics that would contradict the teachings of Stillman and Tonkinson or of Chan, and thereby provide one of ordinary skill in the art of an expectation of success for diagnosis of HPV using a modified version of Meijer wherein the amplified DNA is hybridized to an immobilized HPV-specific oligonucleotide.

Thus, Meijer does not disclose a method for diagnosis of HPV infection comprising the steps set forth in the present claims. Furthermore, the combination of Meijer, in light of Day and Lukhtanov, does not render the steps of the presently claimed method obvious.

Regarding new claims 39 and 40, Meijer does not disclose the HPV probes set forth in SEQ ID NOs: 12 and 13 of the present invention. Thus, Meijer does not disclose a method for diagnosis of HPV infection, which method uses a DNA chip comprising a combination *of each of the HPV nucleic acid sequence probes set forth as of SEQ ID NOs:1-19* attached to a glass slide, at least for the reason that Meijer does not disclose SEQ ID NOs:12 and 13. The combination of Day and Lukhtanov does not remedy this deficiency of Meijer. Therefore, claims 39 and 40 are not rendered obvious under 35 U.S.C. § 103(a) based upon a combination of Meijer, in view of Day and Lukhtanov.

Furthermore, even if a reference or references teaching the HPV probes set forth in SEQ ID NOs:12 and 13 could be found, claims 39 and 40 would not be rendered obvious by the combination of Meijer, in view of Day, Lukhtanov, and such a hypothetical reference or references, at least for the same reasons as discussed above for the rejection of claims 25, 27, 29, 32-34 and 36-37 based upon the combination of Meijer, in view of Day and Lukhtanov.

Accordingly, applicant's respectfully request that the rejection of claims 25, 27, 29, 32-34 and 36-37 under 35 U.S.C. § 103(a) as unpatentable over Meijer, in view of Day and Lukhtanov, be withdrawn.

Claims 31 and 38

The Examiner has rejected claims 31 and 38 under 35 U.S.C. § 103(a) as unpatentable over Meijer *et al* (WO 95/22626, hereafter "Meijer"), in view of Day *et al. Biochem J.* 1990;267:119-123 (hereafter "Day") and Lukhtanov *et al.* (US 6,339,147, hereafter Lukhtanov), as applied to claims 25, 27, 29, 32-34 and 36-37 above, and further in view of Sena *et al.* (US 5,273,881, hereafter "Sena").

As discussed above for the rejection 25, 27, 29, 32-34 and 36-37, Meijer does not disclose a method for diagnosis of HPV infection comprising the steps set forth in the present claims. Furthermore, the combination of Meijer, in light of Day and Lukhtanov, does not render the steps of the presently claimed method obvious.

Sena does not provides teaching to remedy the described deficiencies of the combination of Meijer, in light of Day and Lukhtanov. Specifically, Sena does not provide teaching regarding hybridization kinetics that would contradict the teachings of Stillman and Tonkinson or of Chan, and thereby provide one of ordinary skill in the art of an expectation of success for diagnosis of HPV using a modified version of Meijer wherein the amplified DNA is hybridized to an immobilized HPV-specific oligonucleotide.

Accordingly, applicant's respectfully request that the rejection of claims 31 and 38 under 35 U.S.C. § 103(a) as unpatentable over Meijer, in view of Day and Lukhtanov, and further in view of Sena, be withdrawn.

Claim 35

The Examiner has rejected claim 35 under 35 U.S.C. § 103(a) as unpatentable over Meijer *et al* (WO 95/22626, hereafter "Meijer"), in view of Day *et al. Biochem J.* 1990;267:119-123 (hereafter "Day") and Lukhtanov *et al.* (US 6,339,147, hereafter Lukhtanov) as applied to claims 25, 27, 29, 32-34 and 36-37 above, and further in view of Shalon *et al.* (US 2003/01112695, hereafter "Shalon").

As discussed above for the rejection 25, 27, 29, 32-34 and 36-37, Meijer does not disclose a method for diagnosis of HPV infection comprising the steps set forth in the present claims. Furthermore, the combination of Meijer, in light of Day and Lukhtanov, does not render the steps of the presently claimed method obvious.

Shalon does not provides teaching to remedy the described deficiencies of the combination of Meijer, in light Day and Lukhtanov. Specifically, Sena does not provide

teaching regarding hybridization kinetics that would contradict the teachings of Stillman and Tonkinson or of Chan, and thereby provide one of ordinary skill in the art of an expectation of success for diagnosis of HPV using a modified version of Meijer wherein the amplified DNA is hybridized to an immobilized HPV-specific oligonucleotide. On the contrary, Shalon teaches away from the present invention, in that Shalon teaches that the probes immobilized on the microarray should be at least 50 nucleotides in length (see, for example, paragraphs 61, 64, and 77). In contrast, in the method of the instant invention, the probes immobilized on the DNA chip are only 30 nucleotides in length.

Accordingly, applicant's respectfully request that the rejection of claims 31 and 38 under 35 U.S.C. § 103(a) as unpatentable over Meijer, in view of Day and Lukhtanov, and further in view of Shalon, be withdrawn.

IV. Conclusion

It is respectfully submitted that the amendments and remarks presented here overcome and/or obviate each basis for objection and rejection set forth in the Office Action. The specification and pending claims, as amended, are all believed to be in immediate condition for allowance. Accordingly, the withdrawal of all objections and rejections is respectfully requested. An allowance is earnestly sought.

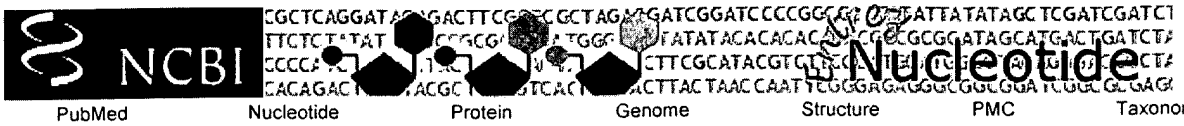
It is believed that no additional fees are required for these submissions. However, should it be found that a fee is required or a refund owed for this application, the Director is authorized to credit any overpayments and/or charge any additional fees during the pendancy of this application to our Deposit Account No. 04-0100.

Respectfully submitted,

Dated: April 7, 2006

By _____

Sarah N. Goldin
Registration No.: 54,127
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant



☐ 1: AF548859. Reports Human papillomavi...[gi:25272157] Links

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  TITLE     HPV L1 ORF sequences from Iran
  JOURNAL   Unpublished
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  AUTHORS   Hamkar,R. and Mokhtari-Azad,T.
  TITLE     Direct Submission
  JOURNAL   Submitted (30-SEP-2002) Virology, School of Public Health and
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            Sciences, Tehran, Iran
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1: Anal Biochem. 2001 Aug 15;295(2):149-57.

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Expression microarray hybridization kinetics depend on length of the immobilized DNA but are independent of immobilization substrate.

Stillman BA, Tonkinson JL.

Schleicher & Schuell, Inc., 10 Optical Avenue, Keene, NH 03431, USA.

Expression microarrays are often constructed by the immobilization of PCR products on two-dimensional modified glass slides or on three-dimensional microporous substrates. In this study we investigate whether the length of the immobilized species and the substrate choice influence hybridization dynamics. Using a simple bimolecular mass action controlled model to describe hybridization, we observed that the extent of hybridization and the initial velocities were directly dependent on the length of the immobilized species. An inflection point was noted at a length of 712 bases, above which the influence of length on hybridization rate decreased. Interestingly, we observed no differences in these parameters whether hybridization occurred on a two- or three-dimensional surface. Furthermore, the affinity of the solution phase labeled species for the immobilized species was identical for all arrayed lengths on both surfaces. These data indicate a similar interaction of the noncovalently immobilized species with either surface. Finally, we have determined that competitive hybridization on expression microarrays is nonlinear with respect to time and concentration of competitor. This observation is critical for analysis of expression array data. Copyright 2001 Academic Press.

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1: Biophys J. 1995 Dec;69(6):2243-55.

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The biophysics of DNA hybridization with immobilized oligonucleotide probes.

Chan V, Graves DJ, McKenzie SE.

Department of Chemical Engineering, University of Pennsylvania, Philadelphia, USA.

A mathematical model based on receptor-ligand interactions at a cell surface has been modified and further developed to represent heterogeneous DNA-DNA hybridization on a solid surface. The immobilized DNA molecules with known sequences are called probes, and the DNA molecules in solution with unknown sequences are called targets in this model. Capture of the perfectly complementary target is modeled as a combined reaction-diffusion limited irreversible reaction. In the model, there are two different mechanisms by which targets can hybridize with the complementary probes: direct hybridization from the solution and hybridization by molecules that adsorb nonspecifically and then surface diffuse to the probe. The results indicate that nonspecific adsorption of single-stranded DNA on the surface and subsequent two-dimensional diffusion can significantly enhance the overall reaction rate. Heterogeneous hybridization depends strongly on the rate constants for DNA adsorption/desorption in the non-probe-covered regions of the surface, the two-dimensional (2D) diffusion coefficient, and the size of probes and targets. The model shows that the overall kinetics of DNA hybridization to DNA on a solid support may be an extremely efficient process for physically realistic 2D diffusion coefficients, target concentrations, and surface probe densities. The implication for design and operation of a DNA hybridization surface is that there is an optimal surface probe density when 2D diffusion occurs; values above that optimum do not increase the capture rate. Our model predicts capture rates in agreement with those from recent experimental literature. The results of our analysis predict that several things can be done to improve heterogeneous hybridization: 1) the solution phase target molecules should be about 100 bases or less in size to speed solution-phase and surface diffusion; 2) conditions should be created such that reversible adsorption and two-dimensional diffusion occur in the surface regions between DNA probe molecules; 3) provided that 2) is satisfied, one can achieve results with a sparse probe coverage that are equal to or better than those obtained with a surface totally covered with DNA probes.

PMID: 8599632 [PubMed - indexed for MEDLINE]

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